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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,100	09/27/2000	David J. Pinsky	0575/51917-C-PCT-US/JPW/J	6042

7590 04/22/2003

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EXAMINER	
DECLOUX, AMY M	
ART UNIT	PAPER NUMBER
1644	12

DATE MAILED: 04/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,100	PINSKY ET AL.	
	Examiner	Art Unit	
	Amy M. DeCloux	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2002 and 10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *21-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-20, drawn to a method for treating an ischemic disorder comprising administering a Factor IXa compound in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the claims of Group I are not independent of the claims of Groups II-V because of the reliance of all the claims of all three groups on the use of a Factor IXa compound as part of their design, operation and effect. The claims of Groups I and III are drawn to a method of treating ischemia and reperfusion injury, respectively comprising administering a Factor IXa compound, while Group V is drawn to a method of inhibiting clot formation comprising administering a mutein of Factor IXa. The traversal is not found persuasive because said three methods have different endpoints and the ingredients of Groups I and III only partially overlap. Applicant further argues that inventions must be distinct and independent. This is not found persuasive because the MPEP clearly shows that the inventions must be independent (see MPEP 802.01, 806.04, 808.01) OR distinct as claimed (see MPEP 806.05-806.05(I))). Applicant contends that there must be a serious burden on the examiner if restriction were not required. However, the examiner notes that MPEP 803 states that: "For the purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation, either separate classification, separate status in the art, or different field of search. Because a search in the non-patent literature of a method comprising the elected group would not be co-extensive with a search of a method comprising all of the non-elected groups, an examination and search of a method comprising all of the groups in a single application would constitute a serious undue burden on the Examiner, and therefore, restriction for examination purposes as indicated is proper.

Applicant's election of the species of Factor IXa mutein, a peripheral vascular disorder, recombinant TPA, plasmin, vascular surgery and a period of time from about 5 days before surgery or onset of the disorder to about 5 days after surgery or onset of the disorder, in Paper No. 12, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the species election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Claims 21-32 have been withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected inventions.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Drawings

Formal drawings and/or photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the attached form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A). Correction of Informalities -- 37 CFR 1.85
New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B) Corrections other than Informalities Noted by Draftsperson on form PTO-948.
All changes to the drawings, other than informalities noted by the Draftsperson, MUST be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings MUST be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

C) Timing of Corrections
Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for treating an ischemic disorder in a subject which comprises administering to the subject a pharmaceutically acceptable form of a Factor IXa compound to treat the ischemic disorder in the patient.

There is insufficient direction or guidance provided to assist one skilled in the art in the selection of any "Factor IXa compound" that are effective for treating any ischemic disorder, nor is there sufficient evidence provided that all such compounds are effective for treating any ischemic disorder, especially in view of the broad definition of "Factor IXa compound" disclosed in the specification. "Factor IXa compound" is disclosed on page 20 to include chemical modifications of Factor IXa, any recombinant mutated form of Factor IXa, nucleic acids, anti-Factor IXa antibodies or fragments thereof, saccharides, ribozymes, small organic molecules or peptidomimetics. It would require undue experimentation to produce all such possible "Factor IXa compound" without more explicit guidance from the disclosure. It would require undue experimentation to investigate all such "Factor IXa compound". The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the method of treating any ischemic disorder when said "Factor IXa compound", broadly encompassed by the claims, are added to the blood administered to a patient.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a mutein's amino acid sequence and still retain the ability to inhibiting clotting but not significantly impair hemostasis, requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Also, minor structural differences among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. For example, minor structural differences among structurally related compounds or compositions, such as amino acid substitutions at one or more of the following amino acids, Ser365, Asp269, and His221 of Factor IXa, can result in substantially different biological or pharmacological activities affecting clot formation and hemostasis as evidenced by Brandstetter et al. (PNAS 92:9796-800, 1995). Given the lack of guidance concerning the nature of the modifications associated with "Factor IXa compound" that the skilled artisan could

use as a guide in making said "Factor IXa compounds"; it would require undue experimentation to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite in that they only describe the compounds of interest by an arbitrary name, "Factor IXa compound" and "inactive recombinant mutein". While the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the protein that the mutein is derived from, and variants thereof. Applicant should particularly point out and distinctly claim what is meant by inactive recombinant mutein by claiming characteristics associated with the protein (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Further, claiming biochemical molecules by a generic name such as "Factor IXa compound" fails to distinctly claim what that protein is and what the compositions are made up of.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

A. Claims 1, 4-8, 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Benedict et al (J. Clin. Invest. (1991) 88:1760-1765).

Benedict et al teach a method for treating an ischemic disorder comprising administering a mutein of Factor IXa which was synthetically formed and integrated into a pharmaceutically acceptable intravenous carrier of saline for the treatment of a peripheral vascular disorder in the mammal (dog) by administering 460 ug/kg in animals of the Wessler stasis thrombosis model, (see entire article, including page 1760, column 2 and page 1761, column 1). Therefore the referenced teachings anticipate the claimed invention.

B. Claims 1, 4, 5, 6, 7, 8, and 15 are rejected under 35 U.S.C. § 102(b) as being anticipated by Moller et al. (CA 2,141,642). Moller et al. teach the use of a factor IXa mutein (a fragment) which does not show coagulation in a method to treat ischemic events in animals of the Wessler stasis thrombosis model (see entire document, including pages 1-2 and page 20, claim 11 as depending on claims 3-10). The instant specification discloses that a mutein encompasses

deletions (page 22, fourth paragraph). Therefore the referenced teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

A) Claims 1, 2, 4-9, 11, 15-17 and 19-20 are rejected under 35 U.S.C. § 103 as being unpatentable over Moller et al. (CA 2,141,642,) or Benedict et al (J. Clin. Invest. (1991) 88:1760-1765), in view of US Patent 5807980.

Moller et al. and Benedict et al teach as above.

Moller et al. teaches it is desirable for antithrombotic therapy to interfere at an early stage of with the coagulation system in order to prevent irreversible processes such as platelet activation, (see entire patent especially page 3, paragraph 3).

Neither teaches the method for treating an ischemic disorder comprising administering a Factor IXa compound and an indirect or direct fibinolytic agent such as TPA or plasmin, respectively. Neither Moller et al. nor Benedict et al teaches said method as applied to a human, nor does either teaches said method as applied to a period of time between five days before surgery or onset of disease, and five days after surgery or onset of disease, nor does either reference teach that said surgery is vascular surgery.

US 5807980 teaches that Plasmin and Tissue Plasminogen Activator (tPA) are fibrinolytic enzymes, and that it is desirable to prevent reocclusion during angioplasty (vascular surgery).

Therefore, it would have been obvious for one of skill in the art to have modified the method for treating an ischemic disorder comprising administering a Factor IXa mutein taught by Moller or Benedict as applied to claims 1, 4-8, 15 and 17 discussed supra, by also administering an indirect or direct fibinolytic agent such as TPA or plasmin, because US 5807980 teaches that Plasmin and Tissue Plasminogen Activator (tPA) are fibinolytic enzymes and because it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combine for their common known purpose. Section MPEP 2144.07.

Further it would have been obvious to modify the method for treating an ischemic disorder comprising administering a Factor IXa mutein taught by Moller or Benedict as applied to claims 1, 4-8, 15 and 17 discussed supra, by applying said method to human vascular surgery, because '980 teaches it is desirable to prevent reocclusion during angioplasty, and because Moller et al. teach the use of a factor IXa mutein (a fragment) which does not show coagulation in a method to treat ischemic events in an animal model of the Wessler stasis thrombosis model.

Further it would have been obvious to apply the methods taught by Moller or Benedict to a period of time between five days before surgery or onset of disease, and five days after surgery or onset of disease because Moller et al. teaches it is desirable for antithrombotic therapy to interfere at an early stage of with the coagulation system in order to prevent irreversible processes such as platelet activation.

B) Claims 1-8, and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Moller et al. (CA 2,141,642, in PTO-1449) in view of Brandstetter et al. (PNAS 92:9796-800, 1995) and Insley et al . (US Patent 4,711,848).

The claims are drawn to a method of inhibiting clot formation in a patient, which comprises adding an inactive recombinant mutein to inhibit clot formation.

Moller et al. teach the use of fragments of factors IX and IXa, which do not show coagulation activity as a method to treat thrombotic diseases encompassed by the claimed methods (see entire document, including pages 1-2 and 20), but do not teach specific amino acid substitutions of Factor IXa.

Brandstellar et al teach the spatial distribution of variants of Factor IXa that have been identified in clinical studies in hemophiliacs, and in particular teaches the catalytic residues SER 365 and HIS 221 that are in the active site of the serine protease(see entire document, especially page 9797, paragraph three). (It is noted that inhibitory recombinant muteins of Factor IXa of said two residues were referred to in the instant specification).

Insley et al. teach the mutant form of alpha-1 antitrypsin (AT) having an arginine substituted for methionine at amino acid position 358 which caused the mutant to convert from an elastase inhibitor to that of a thrombin inhibitor. Additionally, Insley et al. teach recombinant methods of making site specific mutants of AT, the ease of purifying said specific mutants, and that said recombinantly altered forms of AT that could be clinically important for use in inhibiting blood clotting, as for an example, in the treatment of disseminated intravascular coagulation, (entire article, especially column 10, lines 30-40).

Therefore, it would have been obvious for one of skill in the art to have modified the method for treating an ischemic disorder comprising administering a Factor IXa mutein taught by Moller or Benedict, as applied to claims 1, 4-8, 15 and 17 discussed supra, by substituting a Factor IXa mutein that has been recombinantly made, such as a Factor IXa mutein with alterations in the catalytic residues SER 365 and HIS 221 in the active site of Factor IXa that are found in hemophilacs as taught by Brandstellar, because hemophilacs have less clotting ability, and because Insley exemplifies the ease of recombinantly making and purifying mutated proteins involved in blood clotting, and subsequently using them for therapy of disseminated intravascular coagulation.

From the teachings of the reference and of that known and practiced by the ordinary artisan, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 872-9306 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, Ph.D.
Patent Examiner,
April 18, 2003

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